to maintain a somewhat bowed structure.[1]

The above results, which indicate a large disorder in the bound alkyl chain, offer an explanation for the difficulty in building the alkane chain into the crystallographic structure for a difference map.[9] The computed disorder shows a plausible density distribution that nearly has inversion symmetry and even in the crystallographic data, while the drug is slightly bent a near 2-fold symmetry of the electron density is visible.[9] The isoxazole and oxazole groups are quite similar dynamically. However, with the motion of the alkyl chain at the isoxazole end, which appears to sweep out a volume similar to the phenoxy group, the *thermal* volume traced out by the entire molecule is almost symmetrical (see Figure 1). Such a conformational equilibrium superimposed on a binding equilibrium involving a swap of one end for the other accounts for the difficulty in assigning the orientation of the ligand.[9] These motions would then have a direct effect on the binding equilibrium and, therefore, efficacy of the drug.

Acknowledgment. We appreciate many conversations with Professors T. Lybrand, J. A. McCammon, and Dr. A. Tresurywalla. We also thank Prof. M. Rossmann and Dr. J. Badger for communicating X-ray coordinates prior to publication. We thank the Sterling-Winthrop Research Institute, NIH, and the Robert A. Welch Foundation for partial financial support of this work. In addition, we acknowledge a grant of computing time from the San Diego Supercomputing facility as well as the use of our departmental VAX/FPS system, initially purchased with an NSF grant.

(9) Badger, J.; Minor, I.; Kremer, M. J.; Oliveira, M. A.; Smith, T. J.; Griffith, J. P.; Guerin, D. M. A.; Krishnaswamy, S.; Luo, M.; Rossmann, M. G.; McKinlay, M. A.; Diana, G. D.; Dutko, F. J.; Fancher, M.; Rueckert, R. R.; Heinz, B. A. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3304-3308, and private communications with the authors.

Enantioselective Transport through a Silicone-Supported Liquid Membrane

William H. Pirkle* and Elizabeth M. Doherty

School of Chemical Sciences
University of Illinois
Urbana, Illinois 61801

Received February 13, 1989

Tartaric acid derivatives,[1] chiral amine hydrochlorides,[2] chiral crown ethers,[3] and cyclodextrins[4] previously have been utilized as transport agents in enantioselective liquid membranes. To be of practical utility, chiral transport agents must be relatively inexpensive and afford high levels of enantioselectivity. One of the chiral selectors developed in our laboratory[5] meets these requirements and has been used in a single stage bench top prototype membrane device which is capable of affording significant enantiomeric enrichment for appreciable quantities of material.

When swollen with solvent, silicone rubber tubing (Dow-Corning medical grade 0.063 o.d. × 0.030 i.d.) is permeable to even moderately large organic compounds. The membrane device

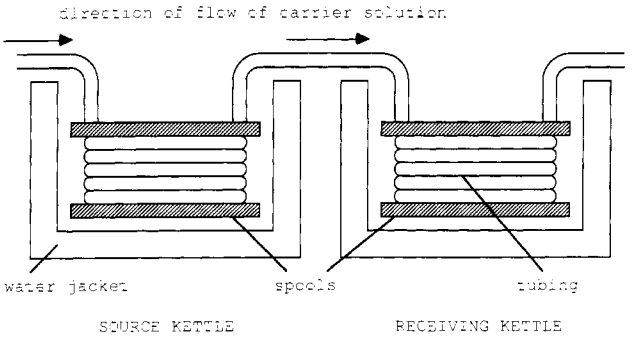

Figure 1. Diagram of the prototype membrane device. The temperature-controlled source and receiving phases are stirred magnetically, while the (*S*)-*N*-(1-naphthyl)leucine octadecyl ester–dodecane solution is slowly recirculated (pump not shown) through the silicone rubber tubing.

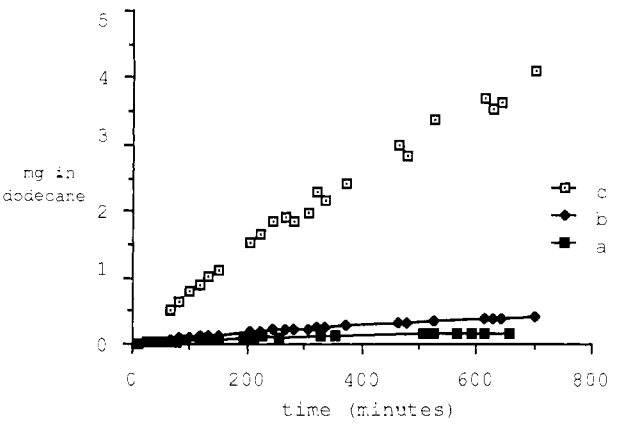

Figure 2. The amount of *N*-(3,5-dinitrobenzoyl)leucine butyl ester present in the dodecane phase (5 mL) as the run progresses. Curve a: no chiral transport agent present. This curve represents each enantiomer. Curve b: The (*R*)-enantiomer when 100 mg of the (*S*)-transport agent has been added to the dodecane. Curve c: The (*S*)-enantiomer when 100 mg of the (*S*)-transport agent has been added to the dodecane.

(Figure 1) consists of 8 ft of tubing wrapped about two spools, each spool being immersed in separate temperature-controlled baths containing 4:1 methanol–water (50 mL). Dodecane (5 mL) is pumped slowly (1 mL/min) through the tubing in a recycle mode. The analyte (50 mg of a racemic *N*-(3,5-dinitrobenzoyl)α-amino ester or amide) is dissolved in the (upstream) source kettle and diffuses slowly through the walls of the tubing. Once in the dodecane solution, the analyte is swept downstream where it can diffuse into the methanol–water in the receiving kettle. The rate of this achiral transport is quite slow; the rate of entry into the dodecane solution at 18 °C is shown in Figure 2.[6] When (*S*)-*N*-(1-naphthyl)leucine octadecyl ester (100 mg) is added to the dodecane, it impregnates the tubing walls, and the rate of transport into the dodecane solution increases. For example, at 18 °C the (*S*)-enantiomer of *N*-(3,5-dinitrobenzoyl)leucine *n*-butyl ester enters the dodecane nine times faster than does the (*R*)-enantiomer. This ratio encompasses both the achiral and the facilitated transport processes (Figure 2). When swept downstream, the analyte diffuses into the 18 °C receiver phase in a 4:1 (*S*):(*R*) ratio; this again represents the summation of the achiral and the chiral transport processes. Here, the presence of the enantioselective transport agent in the dodecane works against the scrubbing process.

Table I presents information concerning the initial rates at which a number of analyte enantiomers were transported into the methanol–water receiving phase when the source and receiving kettles were maintained at 18 °C. Both absolute and relative rates

(1) Prelog, V.; Dumic, M. *Helv. Chim. Acta* **1986**, *69*, 5-11.
(2) Lehn, J. M.; Moradpour, A.; Behr, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 2532, 2534.
(3) (a) Newcomb, M.; Toner, J. L.; Helgeson, R. C.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 4941-4947. (b) Nakazaki, M.; Yamamoto, K.; Tetsumi, I.; Kitsuki, T.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1983**, 787-788. (c) Yamamoto, K.; Noda, K.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1985**, 1065-1066. (d) Yamamoto, K.; Fukushima, H.; Okamoto, Y.; Hatada, K.; Nakazaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1111-1112. (e) Naemura, K.; Fukunaga, R. *Chem. Lett.* **1985**, 1651-1654. (f) Naemura, K.; Fukunaga, R.; Yamanoka, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1560-1561. (g) Naemura, K.; Ebashi, I.; Matsuda, A.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1986**, 666-668. (i) Yamaguchi, T.; Nishimura, K.; Shinbo, T.; Sugiura, M. *Chem. Lett.* **1985**, 1549-1552.
(4) Armstrong, D. W.; Jin, H. L. *Anal. Chem.* **1987**, *59*(*18*), 2237-2241.
(5) Selectors of this type were first prepared in these laboratories by Kris C. Deming for use as a chiral stationary phase for liquid chromatography.

(6) Aliquots of the various phases were analyzed by HPLC using an (*R*)-*N*-(2-naphthyl)alanine-derived CSP of 33% ee. The reduced ee retards the initially eluted (*S*)-analyte and hastens the elution of the (*R*)-analyte, hastening analysis and ensuring more accurate electronic integration.

0002-7863/89/1511-4113$01.50/0

Table I. The Rates of Transport from the Source Phase to the Receiving Phase of Various *N*-(3,5-Dinitrobenzoyl)amino Acid Derivatives

analyte	rate,[a] (*S*)-enantmr	rate,[a] (*R*)-enantmr	ratio of rates	ee (%)
alanine butyl ester	3.8	0.78	4.9	66
valine butyl ester	6.1	1.9	3.3	53
(α-methyl)valine butyl ester	4.4	1.7	2.6	44
leucine methyl ester	5.0	0.71	7.2	76
leucine butyl ester	6.4	1.6	3.9	59
leucine octyl ester	21	12	1.7	26
leucine butyl amide	2.1	0.28	7.6	77
leucine butyl ester (33% *S*-enriched)	10.6	1.5	6.9	75

[a] Rates are in units of μgrams min^{-1} and are relatively constant during the first 25-40% of the run.

of transport change with time as concentrations in the source and receiver phases change. Those rates cited in Table I are for the initial linear portions of the rate curves.

Using the aforementioned analyte, a run in which both kettles were maintained at 18 °C was stopped arbitrarily after 1700 min. The source and receiver phases were evaporated to dryness to afford, respectively, 30.9 mg of 52.4% enantiomeric excess, ee, (*R*)-enriched and 17.4 mg of 57.3% ee (*S*)-enriched analyte after chromatographic removal (silica, methylene chloride) of small amounts of leached transport agent. By lowering the temperature of the source kettle to 0 °C, the rate of the achiral transport process is slowed, while the rate and enantioselectivity of the facilitated process is increased owing to an increase in the association constant of the (S-S) complex; the analyte enters the dodecane solution in a 14:1 (*S*):(*R*) ratio. By raising the temperature of the receiver kettle to 50 °C, the rate of scrubbing increases as diffusion rates increase, and the complex is more extensively dissociated. The net result is that the analyte initially enters the receiving phase in a 9:1 (*S*):(*R*) ratio. By using successive "stages", further enantiomeric enrichment can be obtained. By using 50 mg of 11.5% (*S*)-enriched *N*-(3,5-dinitrobenzoyl)leucine *n*-butyl ester as feed stock, a source phase temperature of 0 °C, and a receiver phase temperature of 60 °C, a 14.2:1 *S*:*R* ratio (87% ee) of analyte enantiomers was observed in the 18 mg of material transported during the first 335 min.

The rate of transport of analyte into the dodecane phase is essentially proportional to the concentration of the transport agent. High transport agent concentrations also increase the enantiomeric purity of the entering material as a larger fraction of the material is transported by the chiral agent. It is evident that the more lipophilic the analyte, the faster the rate of transport and the lower the enantiomeric purity of the initially transported material. A major reason for this is that the rate of the achiral transport process increases with increased tendency of the analyte to partition into dodecane. Increasing the proportion of methanol in the source phase decreases this tendency, slows transport, and significantly increases the enantiomeric purity of the transported material.

The enantioselectivity noted for these complexing agent-analyte combinations in simple liquid-liquid partitioning experiments using dodecane and 4:1 methanol-water somewhat exceeds the separation factors noted for chromatographic separation of these analyte enantiomers on the corresponding chiral stationary phase.[7] This doubtless reflects the effect of the underlying silica and the neighboring strands of bonded phase. However, the differences are not great, and it is doubtful that membrane devices will perform enantiomer separations which cannot be effected chromatographically on the corresponding chiral phase.

Acknowledgment. This work has been supported by grants from the National Science Foundation and from Eli Lilly and Company.

(7) The enantiomer distribution coefficients noted for the analytes in Table I range between 7 and 32 at room temperature. These values assure facile separations of the enantiomers in this series using the various liquid-liquid countercurrent partitioning devices currently available.

Are d^0 ML_6 Complexes Always Octahedral? The X-ray Structure of Trigonal-Prismatic $[Li(tmed)]_2[ZrMe_6]$

Paige M. Morse and Gregory S. Girolami*

School of Chemical Sciences
University of Illinois at Urbana—Champaign
505 S. Mathews, Urbana, Illinois 61801

Received January 17, 1989

Transition-metal six-coordination is dominated by octahedral geometries. Occasionally, complexes that have ligands of significantly disparate sizes or complexes with electronically "noninnocent" chelating ligands exhibit nonoctahedral structures. Examples of such nontraditional complexes are $FeH_2(PR_3)_4$,[1] which has been described as a bicapped tetrahedron, and $Mo(S_2C_6H_4)_3$,[2] which is trigonal-prismatic. *In no case* has a transition-metal complex with six identical unidentate ligands been shown to adopt a nonoctahedral structure.[3] We wish to report the first such example of what may prove to be an entire class of nonoctahedral ML_6 species.

Alkylation of the zirconium phosphine complex $ZrCl_4$(dippe), dippe = 1,2-bis(diisopropylphosphino)ethane, with 2 equiv of dimethylmagnesium in diethyl ether followed by crystallization from pentane yields colorless crystals of the thermally unstable compound, $ZrMe_4$(dippe).[4] The analogous hafnium complex

$$MCl_4(\text{dippe}) + 2MgMe_2 \rightarrow MMe_4(\text{dippe}) + 2MgCl_2$$
1, M = Zr
2, M = Hf

$HfMe_4$(dippe) may be prepared similarly.[5] Surprisingly, the ^1H NMR spectra of the complexes in toluene-d_8 show a *single* resonance for the metal-bound methyl groups that is split into a triplet by coupling to two phosphorus nuclei. The $^{13}C\{^1H\}$ NMR spectra confirm the presence of only a single M-Me environment. The equivalence of the methyl groups is inconsistent with a cis octahedral structure unless there is an unusually low exchange barrier; however, the ^1H and ^{13}C NMR spectra of both compounds are temperature independent and show no broadening even at −80 °C that would suggest the onset of decoalescence. An alternative possibility is that these d^0 complexes are *trigonal-prismatic*. This suggestion would explain the presence of only one methyl environment if the bidentate phosphine ligand bridges between the two triangular faces.

The addition of 6 equivalents of methyllithium to zirconium tetrachloride in diethyl ether followed by filtration and addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmed) yields colorless crystals of the hexamethyl zirconate salt, $[Li(tmed)]_2[ZrMe_6]$.[6]

$$MCl_4 + 6LiMe + 2tmed \rightarrow [Li(tmed)]_2[MMe_6] + 4LiCl$$
3, M = Zr
4, M = Hf

(1) (a) Guggenberger, L. J.; Titus, D. D.; Flood, M. T.; Marsh, R. E.; Orio, A. A.; Gray, H. B. *J. Am. Chem. Soc.* **1972**, *94*, 1135-1143. (b) Meakin, P.; Muetterties, E. L.; Jesson, J. P. *J. Am. Chem. Soc.* **1973**, *95*, 75-85. For other examples, see: (c) Vancea, L.; Bennett, M. J.; Jones, C. E.; Smith, R. A.; Graham, W. A. G. *Inorg. Chem.* **1977**, *16*, 897-902. (d) McNeill, E. A.; Scholer, F. R. *J. Am. Chem. Soc.* **1977**, *99*, 6243-6249.

(2) (a) Bennett, M. J.; Cowie, M.; Martin, J. L.; Takats, J. *J. Am. Chem. Soc.* **1973**, *95*, 7504-7505. For other examples, see: (b) Kepert, D. L. *Prog. Inorg. Chem.* **1977**, *23*, 1-65. (c) Pierpont, C. G.; Buchanan, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 4912-4917. (d) Cowie, M.; Bennett, M. J. *Inorg. Chem.* **1976**, *15*, 1584-1589. (e) Cowie, M.; Bennett, M. J. *Inorg. Chem.* **1976**, *15*, 1589-1595. (f) Draganjac, M.; Coucouvanis, D. *J. Am. Chem. Soc.* **1983**, *105*, 139-140. (g) Colmanet, S. F.; Williams, G. A.; Mackay, M. F. *J. Chem. Soc., Dalton Trans.* **1987**, 2305-2310. (h) Boyde, S.; Garner, C. D.; Enemark, J. H.; Bruck, M. A.; Kristofzski, J. G. *J. Chem. Soc., Dalton Trans.* **1987**, 2267-2271. (i) Tatsumi, K.; Matsubara, I.; Sekiguchi, Y.; Nakamura, A.; Mealli, C. *Inorg. Chem.* **1989**, *28*, 773-780.

(3) We refer specifically to significant changes in the interligand *angles*. There are several solid-state materials such as MoS_2 in which the metal atoms exhibit trigonal-prismatic geometries: Wells, A. F. *Structural Inorganic Chemistry*, 5th ed.; Oxford University Press: Oxford, 1984; p 757.

(4) ^1H NMR (C_7D_8 −60 °C) δ 1.05 (t, J_{PH} = 3.0 Hz, Zr-*Me*).

(5) ^1H NMR (C_7D_8, −60 °C) δ 0.65 (t, J_{PH} = 3.0 Hz, Hf-*Me*); ^{13}C NMR (C_7D_8, −60 °C) δ 49.0 (q, J_{CH} = 110 Hz, Hf-*Me*). Anal. Calcd for $C_{18}H_{44}P_2Hf$: C, 43.2; H, 8.79. Found: C, 42.7; H, 8.75.

0002-7863/89/1511-4114$01.50/0